Epidemiologic Evidence for Workplace ETS As a Risk Factor for Lung Cancer among Nonsmokers: Specific Risk Estimates

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Exposure to environmental tobacco smoke (ETS) among individuals who have never smoked tobacco products has been well established as a risk factor for lung cancer. Most of the epidemiologic evidence for this association has come from studies of exposure to a spouse who smokes. Fewer studies have explicitly evaluated this risk relationship for workplace sources of ETS exposure. These are reviewed here in the context of study design issues and their contributions to the overall evidence for risks of ETS exposure in the workplace. Although most studies have low power to detect workplace risk estimates in the modest range suggested by the larger studies, risk estimates tend to be consistent with those for exposure from a smoking spouse. *Key words*: environmental tobacco smoke, lung cancer, passive smoking. — *Environ Health Perspect* 107(suppl 6):865–872 (1999).
http://ehpnet1.niehs.nih.gov/docs/1999/suppl-6/865-872reynolds/abstract.html

Environmental tobacco smoke (ETS) exposure has been well established as a risk factor for lung cancer in individuals who have never smoked tobacco products (*1–5*). Most of the human health evidence contributing to this conclusion has come from studies of nonsmoking women married to husbands who smoked. The focus on spouses' smoking habits, particularly in studies where women may be more likely to work outside the home, may underestimate the true risk relationship by failing to account for other major daily opportunities for exposure. This is emphasized by a number of exposure assessment studies suggesting that workplace sources of ETS exposure may be as great as the levels measured in households and may also be an especially important source of exposure for some occupational groups (*6–9*). These observations, together with concerns for the possibility of potentiating effects of ETS with other workplace toxicants, argue for a direct estimation of workplace-specific risks. Although there are now dozens of epidemiologic studies evaluating risks for lung cancer in nonsmokers living with spouses who smoke, relatively few have also examined workplace sources of ETS. Two very comprehensive reviews of the literature on ETS and lung cancer, by the U.S. and California Environmental Protection Agencies, include excellent discussions of the evidence for both spouse/household and workplace effects (*4,5*). Both these reviews suggest a consistency of risk estimates for ETS exposure in these various settings. A recent detailed assessment by Wells (*10*) suggests that the best summary estimate of relative risk for lung cancer specific to sources of ETS exposure in the workplace from combined studies is 1.39 (95% confidence interval [95% CI, 1.15–1.68]). In the present article, we give an overview of current epidemiologic evidence from individual studies that have provided specific risk estimates for lung cancer associated with workplace ETS exposures and extend previous reviews by including data from four new studies.

Factors to Consider in Assessing Risk Estimates of ETS Exposure

When evaluating specific estimates of lung cancer risk, it is important to consider various issues in the design of studies involving ETS exposure in the workplace. These issues primarily reflect the general challenges in designing and implementing observational studies, but some have particular relevance for workplace-associated risks. They include a number of factors found in the summary tables in this paper and incorporated in the discussion of their contributions to the question of interest.

Case and control selection criteria are among the most important features of these studies. Almost all the studies with data on workplace exposures have used a case–control study design. Most have selected cases from hospital populations, and only a few have attempted population-based case ascertainment. Because lung cancer in nonsmokers is such a rare event, it is far easier to identify and recruit eligible cases in a hospital setting than in the general population. A particularly important feature of studies of lung cancer is that the cases are correctly classified as having lung cancer. There is considerable variation in the level of diagnostic confirmation in published studies. Among nonsmokers in particular, there is a potential for cancer from other sites that are metastatic to the lung to be misdiagnosed as primary lung cancer. Histologic confirmation levels tend to be higher in hospital-based than in population-based studies. Conversely, hospital studies generally reflect a nonrandom series of patients who agree to interview and seldom contain information on the pool of eligibles from which they were drawn. For the population-based studies, response rates indicate the representativeness of the study sample. Hospital-based studies are subject to potential problems of selection bias but present a much more efficient strategy for case recruitment.

One of the most critical design features of a case–control study is the selection criteria for controls. Hospital-based studies most often recruit controls from other patient groups, including patients with other cancers. To the degree that these reflect smoking-related conditions, controls in these studies may be too similar to the cases with respect to the risk factors of interest. Matching criteria for controls call for a balance between adequate matching to optimize statistical efficiency and avoidance of overmatching, which can result in diminution of power and bias results to the null.

The correct classification of exposure is also an important feature but is not always easy to achieve. Problems in exposure assessment include the choice of study respondents according to smoking history, method of eliciting information, and source of exposure information. Some studies have defined nonsmokers as current nonsmokers; hence they include an unknown proportion of former smokers. More rigorous designs have defined nonsmokers as lifetime nonsmokers. Although the primary method of assessing workplace ETS exposure in the epidemiologic literature has relied on questionnaire rather than on measurement indices, there is considerable variability in how the questions have been posed. For many existing studies, information has been elicited by a single question on workplace exposure. The use of respondent report also poses a particularly difficult problem when studying a highly fatal disease such as lung cancer. Once identified, many patients do not survive long enough to be

This article is based on a presentation at the Workshop on Environmental Tobacco Smoke Risk Assessment held 9–10 July 1998 in Baltimore, Maryland.

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The author acknowledges statistical advice from D. Nelson and helpful comments from J. Samet and M. Jaakkola.

Received 1 March 1999; accepted 28 May 1999.

personally interviewed. As a consequence, most population-based studies rely on information from next of kin. This is a problem especially troublesome for workplace studies. Information on environmental tobacco exposure from the spouse may still be quite valid, especially since the spouse is often the informant, but proxy respondents (generally family members) are much less likely to know about workplace exposures.

It is important to consider that most of the studies with information on risk of exposure to ETS in the workplace were neither explicitly designed to evaluate that association nor to evaluate workplace factors in general. As a consequence they have offered limited information on other risk factors that might mediate the observed associations with ETS. This may be particularly important, as some studies have suggested that passive smokers may differ on a number of potentially relevant characteristics compared to nonsmokers without reported passive smoke exposure (*11–15*). Although diet and family history have been considered in some studies, especially in more recent ones, few have addressed other occupational exposures that might be relevant. Similarily, most include modest numbers of subjects and have very low power to detect a true risk association in a range of public health interests. In the tables that follow, power has been computed for the ability of a study to detect a minimum workplace odds ratio (OR) of 1.4 [from the summary analysis by Wells (*10*)] with an alpha error of 0.05. For U.S. studies (*16,17*) that did not provide information on the prevalence of ETS exposure in controls, prevalence from the U.S. multicenter study was used (*18*). Power was estimated using the formula from Schlesselman (*19*) for studies with an unequal case–control ratio and the formula from Breslow and Day (*20*) for cohort studies.

Epidemiologic Studies with Risk Estimates of ETS Exposure in the Workplace

Hospital-Based Studies in Nonsmoking Women

The most studied population for the influence of ETS on lung cancer has been women classified as nonsmokers. Hospital-based studies with risk estimates of ETS exposure in the workplace in nonsmoking women are summarized in Table 1 (*21–32*). Dating back to the mid-1980s, these studies come from a variety of countries throughout the world. The different settings offer great variability in the prevalence of exposure. Three are from Asian locations, including Hong Kong (*21,23*), Japan (*26*), and Taiwan (*29*), where smoking rates tend to be quite low among women and high among men. The recent study from Russia is particularly interesting, not only because women have traditionally participated in the industrial work force in great numbers but also because of the common consumption of high tar tobacco products (*31*). Only three of the studies are from the United States (*22,24,28*), two of these by Kabat and associates (*22,28*). Most of the observations for nonsmoking populations are nested in larger studies of lung cancer. With the exception of the studies by Koo et al. (*21,23*) and Nyberg et al. (*30*), all used hospital controls.

The two reports by Kabat and colleagues (*22,28*) are part of a larger study of lung cancer conducted in several metropolitan U.S. hospitals. The 1984 report reflects preliminary findings from a group of enrolled cases from whom passive smoking information was elicited late in the course of the study. Subsequent interview protocols were enhanced in a later phase of the parent study to include greater detail on passive smoking. Together these studies suggested a much higher prevalence of ETS exposure at work than at home. The control series employed in the studies by Kabat and colleagues included a large proportion of persons with cancer of other sites, including some cancer types now thought to have an association with tobacco exposure.

Koo and associates (*21,23*) conducted a study of lung cancer patients in Hong Kong hospitals. The later report appears to be an

Table 1. Hospital-based studies with estimates of workplace ETS exposure risks for lung cancer in nonsmoking women.

Figure label	Study, location (reference)	Cases/ controls	Control selection	Workplace measure	Work OR[a]	Spouse OR[a]	Power (%) OR = 1.4
H1	Koo et al., 1983 Hong Kong (*21*)	56/85	Community Match: age,district, SES status	Unknown: use of semi-structured interview	1.0[b]	0.8[b]	25
H2	Kabat and Wydner, 1984, U.S. (*22*)	53/53	Hospital Match: age, race, hospital (60% other cancers)	Current job exposure	0.7[c]	0.8[c]	22
H3	Koo et al., 1984, Hong Kong (*23*)	88/137	Community Match: age, district, SES status	Unknown: use of semi-structured interview	1.2[d]	1.3[d]	19
H4	Garfinkel et al., 1985, U.S. (*24*)	134/402	Hospital Match: age, hospital (colon cancer controls)	> Occasional: last 5 yr Last 25 yr	0.9 (0.7–1.2) 0.9 (0.7–1.2)[e]	1.2 (0.9–1.6) 1.2 (0.9–1.5)	42 25
H5	Lee et al., 1986, England (*25*)	15/158 Married only	Hospital Match: age, hospital, region, ward	Regular exposure (time not specified)	0.6 (15 cases)	0.6 (32 cases)	12
H6	Shimizu et al., 1988, Japan (*26*)	90/163	Hospital Match: age, hospital (56% other cancers)	Smoker in workplace (time not specified)	1.2	1.1	35
H7	Kalandidi et al., 1990, Athens (*27*)	89/118	Hospital Match: admission week (fracture, orthopedics)	Number of smokers in closed space (time not specified)	1.1 (0.2–4.9) Top quartile	2.1 (1.1–4.1)	22
H8	Kabat et al., 1995, U.S. (*28*)	58/139	Hospital Match: age, hospital (61% other cancers)	For four jobs lasting > 1 yr	1.2 (0.6–2.1)	1.1 (0.6–1.9)	26
H9	Ko et al., 1997, Tiawan (*29*)	105/105	Hospital Match: age (outpatients)	Lifetime exposure from coworkers	1.1 (0.4–3.0)	1.3 (0.7–1.9)	20
H10	Nyberg et al., 1998, Sweden (*30*)	89/163	Community Match: age, hospital catchment area	Details from the IARC core questionnaire	1.6 (0.8–3.1)	1.1 (0.6–1.9)	31
H11	Zaridze et al., 1998, Moscow (*31*)	189/358	Hospital Match: hospital (oncology patients)	Jobs in last 20 yr	0.9 (0.6–1.4)	1.5 (1.1–2.2)	46
H12	Boffetta et al., 1998, IARC (*32*)	509/1010	Hospital (5 centers) Community (6 centers) Both (1 center)	Details from a common questionnaire	1.2 (0.9–1.5)	1.1 (0.9–1.4)	93

SES, socioeconomic status. [a]Odds ratios for studies H1–H6 are crude; the remainder adjust for age and other factors. [b]Calculated from Table 4 of the referenced paper. [c]Calcuated from Table 3 of the referenced paper. [d]Calculated from Table 2 of the referenced paper. [e]95% CI has been corrected by Wells (*10*) to be 0.6–1.6.

update of the earlier, but no information is given on the time period for case ascertainment in either. Several features of these investigations make it difficult to assess the impact of a number of potential sources of bias. The number of participating lung cancer patients was estimated by the authors to represent slightly less than 25% of eligible cases, and the authors indicate that cases were drawn primarily from outpatient services. Little information is provided on how community controls were selected. Information was gathered by a semistructured interviewing technique, and the criteria used for classifying workplace exposures are unclear. Both reports suggest null ETS associations with both household and workplace exposures, although the power to detect such an association was quite low. Unlike those in the U.S. studies by Kabat and Wynder (*22*) and Kabat et al. (*28*), the Hong Kong controls reported a high prevalence of household exposure to ETS but very low prevalence of workplace exposure. The null association with household exposure stands in contrast to the significantly positive association reported for spouse exposure in the hospital-based study by Lam et al. (*33*), also conducted in Hong Kong.

Two of the larger hospital-based studies include an early U.S. study by Garfinkel et al. (*24*) and a very recent study from Moscow (*31*). The Garfinkel study retrospectively identified lung cancer cases diagnosed in four U.S. hospitals over the decade from 1971 to 1981. The investigators selected all female lung cancer cases identified as nonsmokers in the hospital records and conducted a careful pathology review and follow-up interviews (primarily with next of kin) on smoking history. Forty percent of women classified as nonsmokers in the hospital records were reported to have smoked at some time. Upon review, it was determined that another 12% were not lung cancer primaries. Patients with colon cancer diagnoses were selected as controls. Analysis of interview information on passive smoking suggested a significantly elevated risk with exposure to a heavily smoking spouse but no association with workplace exposure to ETS reported either within 5 years or 25 years of diagnosis. Workplace exposure to ETS was reported for nearly all controls (87%) for the prior 25 years but only for 20% of controls in the prior 5 years. Zaridze and colleagues (*31*) conducted a study of lung cancer cases diagnosed among female Moscow residents from two cancer treatment centers who had never smoked cigarettes. Controls were drawn from other oncology patients in the two facilities. Although nearly half of the controls (46%) reported exposure to spouse's smoking, only 19% reported workplace exposure. Somewhat elevated risks were noted for exposures to smoking by a spouse, particularly from spouses who smoked "papirosy," but not for workplace exposures. Because the control series included some cancers thought to be smoking-related, analyses were conducted both for the full control series and for a restricted group including only breast and endometrial cancer cases. Results were essentially the same.

Null results for workplace ETS exposures were also reported in a very small subset of married respondents in a multioutcome study in Great Britain (*25*), as well as among nonsmokers in larger lung cancer studies from Greece (*27*), Japan (*26*), and Taiwan (*29*). These studies all had low power to detect an OR as low as 1.4.

Two new European studies present additional detail on workplace-associated risks. The first is a study from Sweden (*30*) in which male and female cases of lung cancer in nonsmokers were drawn from the three major hospitals treating lung cancer cases in Stockholm County. Controls were drawn from population registers for the catchment areas of the three hospitals. Particular attention was directed to confirmation of the subject's smoking status via confirmatory interviews with next-of-kin respondents. This resulted in the identification and inclusion of a small proportion of occasional smokers. Although the overall point estimate for any workplace exposure to ETS did not differ from unity for either men or women, men and women with exposure histories of 30 years or more duration had significantly elevated odds ratios (OR = 2.2; 95% CI, 1.1–4.5). A second measure of dose, years weighted by amount, was also associated with higher risks among those with 30 or more hour-years of exposure (OR = 2.4; 95% CI, 1.3–4.9). These risk associations were adjusted not only for the matching variables but also for occasional smoking, occupational exposure, residence in an urban area, and diet. An interesting finding from the study was the suggestion of a decrease in the OR for ETS exposures (from any sources) with increasing time since exposure. A similar suggestion was made in an earlier study by Akiba et al. (*34*).

One of the most recently published studies is the European multicenter study coordinated by the International Agency for Research on Cancer (IARC) (*32*), which is presented in greater detail in an IARC monograph (*35*). This study, which spanned seven countries (12 data collection centers) and a 7-year ascertainment period, offers the largest total number of cases and controls (males and females combined) to date in a single study with workplace ETS estimates. The study protocol is somewhat of an amalgam of study types, with center-specific variations in a number of design features, including case and control ascertainment criteria. The most important difference cited by the authors was control selection criteria, with five centers using hospital controls, six using community controls, and one using both. Although there were also variations in the interview information collected between centers, they all used a standard questionnaire for ETS exposures. The pooled data analyses suggested only a modest overall effect for any exposure to workplace ETS for all subjects combined (Table 2) and for women (Table 1). Point estimates for all subjects were greater than 1.0 in 8 of the 12 study centers. Analyses using a measure of duration of exposure (level × hours/day × years), however, suggested significant increasing risk with increased exposure (p for all subjects = 0.01, p for women only = 0.03). As in the Swedish study (*30*), which included some subjects also included in the IARC study, a suggestion of decreasing risk with increasing time since last exposure was also noted. Workplace point estimates did not differ substantially from those for spouse exposures.

In general, the hospital-based studies offer a balance of strengths and weaknesses to this area of research. Most, because of their case selection criteria, do not include proxy interviews and hence include only information directly from the respondent of interest. Additionally, the use of hospital controls is likely to reduce the problem of differential recall bias. Conversely, these studies have greater propensity for selection bias and the common use of cancer controls (particularly for other cancers that may be smoking related) may tend to bias risk estimates toward the null. This is of special concern in these studies because of the evidence that ETS may be associated with a broader group of cancers than was previously believed based only on risk relationships for active smoking (*36–38*). Unfortunately, because of limited information reported in the publications, it is not possible to systematically compare many of the features of protocols employed. Most studies do not specify the time period covered by ascertainment, the amount of retrospective ascertainment, or the temporal concordance of case and control selection. These timing issues may be of consequence, as the prevalence of active smoking has declined in many areas and workplace restrictions on smoking have become more common. Tremendous differences between studies are evident in the assessment of workplace ETS exposure, but less detail is given for this than for household assessments. Most studies report only crude OR estimates or offer limited adjustment for other factors. In addition small sample sizes make it unlikely that such studies would be able to reliably detect elevated risk relationships if they exist.

The large IARC study (*32,35*) builds on both the general strengths and weaknesses of hospital-based studies. This study, along with the Swedish report (*30*), represents one of the few studies that has had an opportunity to comprehensively elicit information on a wide spectrum of parameters of lifetime exposures to ETS. Observations from this effort suggest modest risk associations that may vary with time since exposure.

Population-Based Studies in Nonsmoking Women

There are far fewer population-based studies (*17,18,39,40*) of this extremely rare health outcome (Table 3). This is not surprising, given the labor-intensive efforts required to fully ascertain all eligible cases quickly enough to invite these individuals to participate in a personal interview. Lung cancer in lifetime nonsmokers comprises an estimated 10% of all lung cancers in U.S. women and a much smaller proportion of lung cancers in men (*22,41*). With the exception of one study from northeastern China (*40*), all the population-based studies with risk estimates of ETS exposure in the workplace for nonsmoking women have been conducted in the United States. The strength of the evidence for risks of ETS exposure in the workplace between these few studies, however, is quite variable.

In a Los Angeles study designed to evaluate lung cancer risk factors by cell type, Wu and colleagues (*39*) separately evaluated ETS risk relationships for the small subset of women who had never smoked tobacco products. With regard to characterizing workplace-associated risks, this study suffered from small sample size, low response rates, the limitation of excluding proxy respondents, use of telephone interviewing, and control selection from neighborhood matching (which might tend to overmatch by socioeconomic status, and hence workplace exposure opportunity).

Table 2. Studies with estimates of workplace ETS exposure risks for lung cancer in nonsmoking men or men and women combined.

Study, location (reference)	Cases/ controls	Control selection	Workplace measure	Work OR (95% CI)[a]	Spouse OR (95% CI)[a]	Power (%) OR = 1.4
Kabat and Wynder, 1984, U.S. (*22*)	25/25 Men	Hospital Match: age, race, hospital (60% other cancers)	Current job exposure	3.3	1.0	14
Lee et al, 1986, England (*25*)	10/98 Men	Hospital Match: age, region, ward	Regular exposure (time not specified)	1.6	2.5	11
Butler et al., 1988, (*48*)	7 cases 13, 575 P-Y Men	Cohort Seventh Day Adventists (includes smokers)	Work with smoker 1–10 yr 11+ yr	1.7 (0.2–6.7) 0.0	0.0 1.2 (0.2–8.8)	5
Janerich et al., 1990, New York (*16*)	191/191 Men Women	Community Match: age, sex, county (from DMV records)	150 P-Y of exposure	0.9 (0.8–1.04)	0.9 (0.6–1.6)	47[b]
Kabat et al., 1995, U.S. (*28*)	41/117 Men	Hospital Match: age, hospital (61% other cancers)	For four jobs lasting > 1 yr	1.02 (0.5–2.1)	1.6 (0.7–3.8)	22
Nyberg et al., 1998, Sweden (*30*)	35/72 Men	Community Match: age, hospital catchment area	Detail from the IARC core questionnaire	1.9 (0.5–6.7)	2.0 (0.7–5.4)	14
Boffetta et al., 1998, IARC (*32*)	650/1540 Men + Women	Hospital (5 centers) Community (6 centers) Both (1 center)	Detail from a common questionnaire	1.2 (0.9–1.5)	1.2 (0.9–1.4)	97
Jockel, 1998, Germany (*49*)	17/236 Men + Women	Community "Individually matched" (criteria not specified)	Questionnaire "compatible" with IARC instrument	2.7 (0.7–9.7) "High" exp	1.9 (0.5–7.7) "High" exp	24[c]

Abbreviations: DMV, Department of Motor Vehicles; exp, exposure; P-Y, person years. [a]Crude or only age-adjusted odds ratios are available from most of the studies (*16,22,25,32,48*). Some of the more recent studies (*28,30,49*) also adjust for other factors. [b]Exposure prevalence in controls unknown—prevalence from Fontham et al. (*18*) used. [c]Based on exposure prevalence reported for workplace and other sources of ETS.

Table 3. Population-based studies with estimates of workplace ETS exposure risks for lung cancer in nonsmoking women.

Figure label	Study, location (reference)	Cases/ controls	Control selection	Interview	Percent proxy	Path. conf. (%)	Response rate (%)	Work OR (95% CI)[a]	Spouse OR (95% CI)[a]	Adjustments	Power (%) OR = 1.4
P1	Wu et al., 1985, Los Angeles (*39*)	31/92	Neighborhood Match: birth-year	Phone	0	100	49	Adeno: 1.3 (0.5–3.3) Squam: 2.3 (0.7–7.9)	Adeno: 1.2 (0.5–3.3) Squam: 1.0 (1.0–7.6)	Age + location	18
P2	Wu-Williams et al.,1990, NE China (*40*)	415/602	Community Match: age	In person	0	74	92	1.1[a]	0.7	Age + others	84
P3	Brownson et al., 1992, Missouri (*17*)	432/1166	Community DMV/HCFA Match: age	Phone	65	76	70	1.2 (0.9–1.7) Highest quartile	1.3 (1.0–1.7) Highest quartile	Age + previous lung disease	89[b]
P4	Fontham et al., 1994, U.S. multi-center (*18*)	609/1247	Community RDD/HCFA Match: age, area	In person	36	100	74	1.4 (1.1–1.7) 1.6[c] (1.2–2.0)	1.3 (1.0–1.6)	Age + others + other ETS	95

Abbreviations: adeno, adenocarcinoma; path. conf., pathologic confirmations; DMV/HCFA, controls drawn from the files of the Department of Motor Vehicles and Health Care Financing Administration; RDD/HCFA, controls drawn from random digit dialing and files of the Health Care Financing Administration; squam, squamous cell carcinoma. [a]Corrected OR from Wells (*10*) is 1.2, with a calculated 95% CI of 0.9–1.6. [b]Exposure prevalence in controls unknown; prevalence from Fontham et al. (*18*) used. [c]Data from reanalysis by Reynolds et al. (*51*) excluding nonworking women and adjusting for other sources of ETS.

A subsequent study by the same investigator in China (*40*) was also unlikely to provide strong evidence for ETS-associated risks because of the very strong risk associations that have been observed for home heating and cooking practices (*40,42–44*). In a small Denver study of adenocarcinoma of the lung (not tabled) that included 19 cases in nonsmoking women. Brownson et al. (*45*) reported a suggestively elevated OR associated with 4 hr or more of daily passive smoke exposure from household and workplace sources combined (OR = 1.7; 95% CI, 0.4–3.0). This study reported no increased risk for living with a spouse who smoked, but information was not presented separately for household or workplace exposures. The Missouri study by Brownson and associates (*17*) drew subjects from a study of current nonsmokers (never smokers and former smokers) that was designed primarily to evaluate radon-associated lung cancer risks among women with a low prevalence of work outside of the home in a residentially stable community (*46*). Respondents in that study were interviewed by telephone rather than in person, and roughly two-thirds of the interviews were obtained from a proxy. A population-based Florida study (not tabled) providing one of the highest point estimates for spouse effects reported that there was no association between workplace ETS exposure and lung cancer in nonsmoking women but did not present any specific risk estimates (*47*). The only study in this group, which was designed explicitly to investigate the relationship between ETS exposure and lung cancer, was the Fontham et al. study (*18*). Conducted in five U.S. collaborating centers, it is the only study of the population-based group to report a statistically significant elevated risk of lung cancer in nonsmoking women exposed to ETS in the workplace. Although modestly higher than the point estimate for spouse exposures in this study, the workplace OR is well within the CI for the spouse estimate.

Studies Including Nonsmoking Men

Only a few studies (*16,22,25,28,30,32,48,49*) offer risk estimates for nonsmoking men (Table 2). They include three older hospital studies, the two studies by Kabat et al. (*22,28*) and the study by Lee et al. (*25*) discussed above, which presented separate analyses for men and women. The number of men in these studies is even smaller than the number of women, and the power to detect an OR of 1.4 is less than 12% for each. A small cohort study of California Seventh Day Adventists, with only seven lung cancer cases in men (and six in women), had insufficient power to detect stable workplace risk estimates (*48*). In addition, although most Seventh Day Adventists do not smoke, the cohort study was not restricted to nonsmokers and hence included a small proportion of active smokers. A population-based study by Janerich et al. (*16*) covering 23 counties in the state of New York evaluated ETS-related risks in a group of current nonsmokers. Of these, 191 cases and individually matched controls (drawn from New York Department of Motor Vehicle records) were identified as lifetime nonsmokers. This study found no evidence of workplace-associated ETS risks but also reported little or no association with adult household exposures. Unfortunately, risk estimates were not presented separately for men and women. In a recent report from the American Cancer Society's large prospective Cancer Prevention Study II (*50*), ETS exposure in the workplace was not associated with lung cancer mortality, but no specific risk estimates were given.

Also included are three recent European studies, those from Sweden (*30*) and Germany (*49*), and the IARC multicenter study (*32*). The Swedish and IARC studies, which provide separate workplace point estimates for women (who constitute the majority of cases among never smokers), are discussed in some detail above. The German study, also included in the IARC multicenter study, presents separate point estimates for lifetime nonsmokers and occasional smokers. Among men and women combined classified as never smokers, point estimates for high exposures to ETS from a spouse (OR = 1.87; 95% CI, 0.45–7.74) or from the workplace (OR = 2.67; 95% CI, 0.74–9.67) were both elevated, although with wide CI values in this small sample. Further adjustment for dietary factors had little effect on the risk estimates from this study. Point estimates for men only, or for men and women combined in these studies, were similar to those for women only when reported separately.

The generally null results and low power from this group of studies provide little additional information on workplace risks from ETS exposure. To remove any sex-related bias, the remainder of this article will focus on studies of women only.

Studies with Exposure–Response Estimates

Only five studies present estimates for exposure–response effects from ETS (Table 4). Two of these, the small British study by Lee et al. (*25*) and the more recent study of Kabat et al. (*28*), provide risk estimates for qualitative measures of exposure. Neither of these studies observed an overall effect for workplace ETS exposure, and neither provides strong evidence for an exposure–response effect. Exposure–response estimates for a quantified exposure measure are available from the U.S. (*18*) and IARC (*32*) multicenter studies, as well as from the

Table 4. Studies with workplace ETS dose–response estimates for nonsmoking women.

Study (reference)	Exposure level	Odds ratio (95% CI)	Adjustment
Qualitative assessments			
Lee et al., 1986 (*25*)	Not at all	1.0	Age, spouse smoking, marital status
	Little	1.2	
	Average/a lot	0.0	
Kabat et al., 1995 (*28*)	Low	1.0	Age, education, hospital type
	Intermediate	0.9 (0.4–2.1)	
	High	1.4 (0.6–2.8)	
Quantitative estimates			
Fontham et al., 1994 (*18*)	Years of exposure		
	0	1.0	Age, race, study area, dietary factors, family history of lung cancer, high-risk occupations
	1–15	1.3 (1.01–1.7)	
	16–30	1.4 (1.04–1.9)	
	> 30	1.9 (1.2–2.8)	
		p for trend = 0.001	
Reynolds et al., 1996 (*51*)	0	1.0	All of the above plus other sources of ETS exposure. Referent excludes nonworking women.
	1–15	1.5 (1.1–1.9)	
	16–30	1.6 (1.1–2.2)	
	> 30	2.1 (1.4–3.2)	
		p for trend < 0.001	
Boffetta et al., 1998 (*32*)	Years of exposure		
	0	1.0	Age
	1–29	1.1 (0.9–1.5)	
	30–38	1.5 (0.9–2.4)	
	> 39	1.2 (0.7–2.3)	
		p for trend = 0.10	
	Level × hr/day × yr		
	0	1.0	
	0.1–46.1	1.0 (0.8–1.4)	
	46.2–88.9	1.1 (0.7–1.8)	
	> 89.0	1.9 (1.1–3.2)	
		p for trend = 0.03	

new Swedish study (*30*). Data from the U.S. study in Table 4 are drawn from the original publication of the full multicenter study results (*18*) and from a follow-up analysis that included only working women and further adjustment for other sources of adult ETS exposure (*51*). The latter analysis, although presenting slightly higher point estimates of risk, provided results that are statistically indistinguishable from those of the original paper. Data from this study suggest a doubling of risk for women reporting 30 or more years of workplace ETS exposure. The IARC study (*35*) provides risk estimates for years of workplace exposure as well as for a duration measure incorporating years and amount (level and hours per day). Only the latter measure suggests a dose–response trend, largely because of the nearly 2-fold risk at the highest category of exposure. Results in Table 4 are those reported for women only, but the relationship is similar to that for all subjects combined. The Swedish study (*30*) (not tabled) does not present data separately for women but suggests about a doubling of risk for subjects with more than 30 years of reported workplace exposure.

Additional Observations

A number of studies that did not directly examine risk estimates for workplace ETS exposure nonetheless offer relevant observations on risk estimates from spouse exposure, stratified by occupational or residential characteristics. The study by Akiba et al. (*34*) of lung cancer in nonsmoking women in the cohort of atomic bomb survivors followed by the Radiation Effects Research Foundation noted substantially higher risk estimates for heavy ETS exposure from spouses among women who were employed as blue-collar workers (OR = 10.4; 95% CI, 1.6–66.7) than among women employed in white-collar occupations (OR = 1.6; 95% CI, 0.6–4.1) or among women who were housewives (OR = 1.5; 95% CI, 0.7–3.3). This association suggested broader exposure to ETS from other sources in addition to spouses in these lower socioeconomic groups where smoking is more prevalent.

Studies based on self-report and biomarkers have shown that a nonsmoker married to a smoking spouse is more likely to be exposed to tobacco smoke in other settings as well (*52,53*). Similar findings from an earlier study from Stockholm County, Sweden (*54*) indicated that risk estimates were higher for women exposed both at home and at work than for women exposed in only one setting. A somewhat contrary observation in a small mortality study from Pennsylvania (*55*) found that women who did not work outside the home had higher risks for lung cancer mortality with exposure to a smoking spouse (OR = 1.9) than women who worked outside the home (OR = 0.8).

In his landmark cohort study of over 91,000 women, Hirayama (*56*) observed that risk estimates for spouse exposure tended to be higher among women living in more rural areas. He attributed that association to the fact that rural couples experienced longer periods of mutual contact than couples in urban environments. Likewise, an occupational mortality study from China reported higher lung cancer standard mortality ratios for women who did not work outside the home than among working women (*44*). These mortality studies may be subject to a healthy worker bias, since the lung cancer decedents may have been less likely to be employed at the time of their death. As a group these studies provide indirect and ill-defined evidence at best for the effects of workplace ETS exposures.

Issues Addressed by the U.S. Multicenter Study

Because the U.S. multicenter study reported by Fontham and associates (*18*) was specifically designed to address some of the methodologic limitations of earlier studies of passive smoking and lung cancer, design features of the study are considered in detail. It was designed as a single study, with a single protocol, conducted in a small number of closely collaborating centers. Although some of the features of this study were incorporated into earlier efforts, the combination was unique to the multicenter study. Issues of importance include:

- Misclassification of smoking status. Because of the powerful effect of active smoking on lung cancer risk, inclusion of former smokers in studies of this type poses a potentially serious source of bias in assessing the effects of ETS exposure. The U.S. multicenter study employed a number of strategies to minimize this problem. First, a three-tiered approach was used in assessing the smoking status of the cases: medical records review, physician query, and respondent report. Respondent information for both cases and controls was obtained first in a screening interview and again in a more in-depth interview. In addition, for both cases and controls, urine cotinine analyses were employed to eliminate misreported current smoking. This latter procedure resulted in the exclusion of two cases and 25 controls with urinary cotinine measures of 100 ng/mg or higher who reported themselves to be lifetime nonsmokers. Finally, the study employed a rapid case ascertainment procedure to limit the number of proxy interviews required.
- Histopathologic specificity. Because of the interest in whether certain cell types of lung cancer, particularly Kreyberg II tumors (squamous cell, large cell, and small cell carcinomas), may be more likely to be linked with tobacco exposure, the Fontham et al. study (*18*) was designed to have a sufficiently large sample size to separately estimate ETS risks for the adenocarcinomas and other cell types combined. Pathology slides for the study cases were submitted for independent review by the study pathologist. This review resulted in the further elimination of ten cases otherwise eligible (two benign lesions, three metastatic carcinomas, and five other types of cancer) for the study, and a more detailed classification of lung cancer cell types for the study cases.
- Recall bias. Because of the potential for recall bias in studies of a serious and fatal disease using healthy controls, the study by Fontham et al. (*41*) incorporated two control groups during the initial years: colon cancer controls and population controls. In an initial evaluation of study results, risk estimates were comparable for the two control groups, so the colon cancer control series was discontinued for the remaining years of the study.
- Source of ETS exposure. Because the primary hypothesis of interest for this study related to passive smoking, the major thrust of the questionnaire was a detailed assessment of exposure to ETS. This included an extensive series of questions to assess timing of exposure, quantity of exposure, and sources of exposure for the lifetime of the respondent.
- Confounders and other risk factors. To estimate ETS-associated risks for lung cancer without potential for confounding, the Fontham study was designed to collect a broad spectrum of potentially important covariables and a sufficiently large sample size to conduct multivariate analyses. Point estimates for ETS exposure risks were presented with adjustments not only for age, race/ethnicity, educational status and study area, but also for dietary factors, family history, and employment in putatively high-risk occupations.

Many of these same issues also were addressed in the IARC European multicenter study (*32*), although with less consistency between study centers. There was a fair amount of variability in the study protocol from center to center, which also yielded some heterogeneity in point estimates between centers. Nonetheless, this very large study provides the first stable point estimates for Western European populations and provides some valuable additional methodologic information. Although active smokers were also recruited in many of the study centers, the analysis presented by Boffetta and

colleagues was restricted to individuals who reported not smoking more than 400 cigarettes in their lifetime. Validation studies on active smoking status were carried out in three of the centers via confirmatory interviews with next of kin. Data from this effort suggested a misclassification rate of only 1.2%. Histologic confirmation was obtained for 76% of the cases. Roughly half the study centers used hospital controls and half used community controls. Separate analyses with each type of center suggested no difference in ETS effects. Similar to the Fontham study, the IARC study paid special attention to detailed ETS exposure histories including information on timing, dose and sources, and included (in some study centers) a wide spectrum of covariables.

Summary

Of the many studies published to date that provide some evidence for ETS-associated risks for lung cancer in nonsmokers, few have explicitly addressed workplace sources of ETS exposure. The hospital-based and population-based studies that provide specific workplace ETS point estimates for nonsmoking women are summarized in Figure 1. Estimates of the ORs, with their respective 95% CI values (if provided by the authors), are plotted against the power to detect a minimal OR of 1.4. Only three studies have greater than 85% power to detect an odds ratio of that magnitude: the Missouri study by Brownson and colleagues (*17*) and the large U.S. and European multicenter studies (*18,32*). Each of these suggests an elevation of risk, although only the point estimate from Fontham et al. (*18*) has a 95% CI that excludes 1.0.

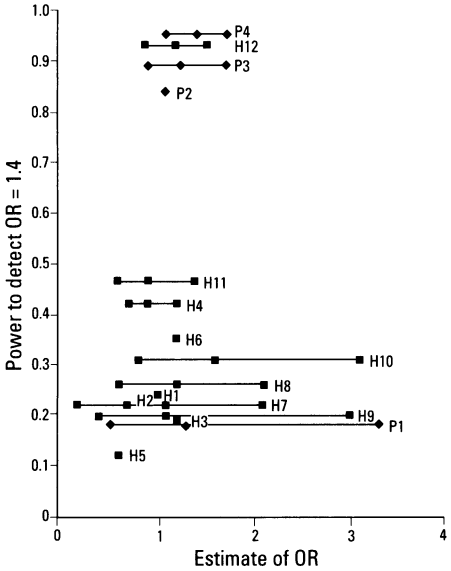

Figure 1. Workplace ETS exposure risk estimates from studies of nonsmoking women. Point estimates are presented for the odds ratio and where available by the authors, 95% confidence interval. Squares represent hospital-based studies and are referenced to studies H1 through H12 from Table 1. Diamonds represent population-based studies and are referenced to studies P1 through P4 from Table 3. These values are from the original publications and do not incorporate the recent corrections from Wells (*10*) that are noted on the tables.

It is noteworthy that the workplace risk estimates across studies tend to be consistent with those from exposure to a smoking spouse. This consistency raises the important issue of exposure opportunities by source and setting. National survey data for 1995 suggested that roughly a quarter of nonsmoking work force members are exposed to ETS by their co-workers (*57*). This estimate is similar to that from California's baseline tobacco survey at the beginning of the decade (*58*), before statewide smoking bans were legislatively mandated. Notably, however, the prevalence of reported workplace exposure has been very much a function of workplace smoking policy. Among nonsmoking Californians who worked indoors between July 1990 and June 1991, 31% reported ETS exposure at work. This ranged from 52% exposed in workplaces with no smoking restrictions, to 50% in workplaces with minor restrictions, to 24% in workplaces prohibiting smoking in the work area, to 10% in workplaces where there was a total ban on smoking. Additionally, since a number of studies suggest that certain occupational groups may have unusually high workplace ETS exposure (*6–9,59*), questions of workplace-associated risks need to incorporate better exposure information than is traditionally available from epidemiologic studies on this topic.

The limits of human health studies to detect small and difficult-to-measure risks, as is the case for ETS, was eloquently discussed in the editorial accompanying the recently published IARC study of ETS and lung cancer (*60*). The human health evidence from epidemiologic studies provides only one piece of the puzzle in this regard. Together with exposure and biomarker information, the evidence suggests that exposure to ETS, whether at home or at work, is a risk factor for lung cancer among nonsmokers.

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